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Advances in Treating Vasovagal Neurocardiogenic Syndrome: A Comprehensive Review of Medical Interventions

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Abstract

Neurocardiogenic vasovagal syndrome (VVS) is a common clinical condition that results in a transient loss of consciousness and inability to maintain posture, with a rapid and spontaneous recovery. Considering the technological advances regarding the effectiveness of different treatments for VVS, this article aims to review the treatment options available in the medical literature to better understand the treatment options and their potential benefits. This study is a literature review of the medical literature focused on publications from 2005 to 2022 related to the therapeutic management of VVS. Digital databases such as PubMed and SciELO were searched using the descriptors “vasovagal syncope”, “neurocardiogenic syncope” and “treatment of vasovagal syncope” to identify relevant studies. Orthostatic training (or tilt training) is a non-pharmacological approach that involves postural training performed through multiple sessions of orthostasis. Tilt training (TTr) proved to be an effective therapeutic method with long-term benefits in refractory patients. Pharmacological treatment should be considered in a case-by-case scenario. Cardioneuroablation is a procedure that has been shown to eliminate or significantly reduce the vagal response, leading to symptom relief in up to 75% of patients. Results showed that implementing a definitive pacemaker reduced symptoms in at least one-third of patients. In summary, treatment strategies for VVS are evolving with advances in medical research, allowing for a thorough analysis of each modality to determine its suitability. It is crucial to emphasize that the selection of treatment options should be evaluated by a specialist individually to ensure effective management of the patient’s clinical manifestations. Thus, available interventions have the potential to improve patient’s quality of life significantly.

Keywords: vasovagal syncope, neurocardiogenic syncope, treatment of vasovagal syncope, orthostatic training, pharmacological treatment, tilt training, cardioneuroablation, pacemaker, medical literature review

1. Introduction

Neurocardiogenic vasovagal syndrome (VVS) is a common clinical condition resulting in a transient loss of consciousness and an inability to maintain body posture, with rapid and spontaneous recovery. Its etiology is characterized by being mostly prevalent in women, particularly during youth, and being strongly linked to underlying psychological stressors (Sheldon et al., 2015). The 2015 Heart Rhythm Society Expert Consensus defines VVS as a syncope lacking specific clinical features. It presents a challenge to clinicians and patients, with recurrent episodes of the syndrome potentially resulting in physical injury with serious outcomes (such as increased risk of fractures) and psychological distress. The most common manifestation of VVS is syncope, which may or may not be accompanied by clinical signs such as sweating, weakness, nausea, heat, headache, dizziness, blurred vision, and palpitations (Ali et al., 2021).

Regarding non-invasive forms of treatment, medications can be prescribed to prevent the sudden drop in blood pressure and the resulting syncope (with adequate hydration being an important adjuvant), but there is no specific pharmacotherapeutic approach that acts directly on the condition. Orthostatic training (or tilt training) is a non-pharmacological approach entailing postural training performed via multiple orthostatic sessions (Gajek et al., 2006). Management of the syndrome focuses mainly on behavioral care, such as avoiding and controlling the settings and situations that can trigger it (Abuzainah et al., 2022). In addition, aerobic physical training (APT), a

supervised physical training program, can be employed.

Throughout the 1990s, cardioneuroablation emerged as a potential treatment for patients with vasovagal neurocardiogenic syndrome who do not respond to preventive measures and pharmacological management (Lakkireddy, 2019; Gampa & Upadhyay, 2018). Cardioneuroablation is a catheter ablation procedure that denervates the vagus nerve. This treatment has shown improved safety and efficacy compared to previous invasive approaches, such as pacemaker implantation, with less significant outcomes and high rejection rates among young patients.

In light of technological advances regarding the efficacy of different neurocardiogenic vasovagal syndrome (VVS) treatments, this article aims to comprehensively review the available therapeutic options based on the medical literature. This review analyzes the safety and efficacy of pharmacological and non-pharmacological interventions cited above. Thereafter, it is intended to provide a better understanding of the various treatment options for VVS and their potential benefits.

2. Method

For a literature analysis of the medical literature, priority was given to publications from 2002 to 2022 that address the therapeutic management of vasovagal neurocardiogenic syndrome, which were accessed between late January and early February 2023. The research for scientific articles in bibliographic sources was developed through the PubMed and SciELO databases, using the descriptors “vasovagal syncope”, “neurocardiogenic syncope” and “treatment of vasovagal syncope”. Inclusion criteria were articles consisting of randomized clinical trials and meta-analyses, with scientific texts in English, Portuguese, Chinese, and Spanish. This paper was guided by the research question elaborated from the “PICO” strategy by assessing “P” (population) as those who have the syndrome, “I” (intervention) on the most qualified treatments, “C” (control) as the ways in which the management works and “O” (outcome) on the effectiveness of the treatments observed. In addition, the quality of the research was determined by the Overview Quality Assessment Questionnaire platform. After applying all criteria, only 21 studies were included for further analysis.

3. Results

3.1 Non-pharmacological treatment

3.1.1 Aerobic physical training (APT)

A study on supervised aerobic physical training (APT) found a positive effect in its test group, resulting in a significant increase in maximal oxygen uptake and a reduction in positive tilt tests (Takahagi et al., 2014). Specifically, after a 12-week intervention period, 72.7% of the test group had negative results for syncope at reassessment. These findings suggest that supervised APT may be an effective intervention to increase tolerance time in the orthostatic position.

3.1.2 Tilt training

Tilt training (TTr) is an effective therapeutic method with long-term benefits for patients with refractory symptoms, leading to improved tolerance to orthostasis due to increased vasoconstrictor reserve and a reduction in its variability. A randomized clinical trial involving 28 patients found a reduction in the mean number of vasovagal syncope recurrences (from 4.0 to 3.2 syncopal episodes/year/patient), with a 19% relative decrease in the recurrence rate (Laranjo et al., 2012).

Tilt training is a prevalent treatment, which consists of tilting the body of patients with vasovagal syndrome and can be performed even by the patient at home, leaning on the wall or squatting the body until the tilt angle becomes intolerant. This technique has shown an excellent prognosis in reducing syncope in the daily life of this group of patients, according to several studies in the medical literature (Kisanuki et al., 2022; Jang et al., 2013; Hussain et al., 2021). The only requirements for performing this treatment are: having an accurate diagnosis of the syndrome, educative projects done by medical professionals, and at-home training done by the own patients.

3.2 Pharmacological treatment

The most effective pharmacological treatment for recurrent vasovagal syncope is still elusive (Schleifer & Shen, 2015). Many commonly used drugs have questionable efficacy, pose severe risks of possible adverse effects, and are only considered on a case-by-case basis. A Cochrane review on the pharmacotherapy of vasovagal syncope revealed insufficient evidence to generalize the use of any pharmacological agent to treat VVS (Romme et al., 2011).

3.2.1 Fludrocortisone

While most synthetic corticosteroids have some mineralocorticoid activity, only fludrocortisone is exclusively a mineralocorticoid. As such, this aldosterone analog has received the most attention among potential drugs that may intervene in syncope by modulating blood volume and is likely to be most effective in individuals with a partial response to hydration and salt supplements, as well as in patients with hypotension. In a randomized clinical trial, despite not reaching the pre-established target of a 40% reduction in the incidence of events, daily administration of a 0.2mg dose of the drug demonstrated a significant reduction in the propensity for new episodes of syncope to occur (Sheldon et al., 2015).

3.2.2 β-blockers

Regarding sympathetic nervous system (SNS) activity, vasovagal syncope is believed to be caused by an SNS reaction that causes a rapid spike in catecholamines before the onset of syncope. β-blockers have often been employed to prevent syncope, hoping that they may attenuate the reflex via a decrease in catecholamine release or attenuation of target organ effects.

β-blockers are a heterogeneous group of pharmaceutical substances that act as β-adrenergic receptor antagonists. While specific drugs, such as atenolol and metoprolol, are selective for the β1 receptor, others are not. Propranolol is a widely studied non-selective β-blocker characterized by its lipophilicity, allowing its passage through the blood-brain barrier. Its ability to exert more expressive effects on the central nervous system than other agents of the same class is well established.

Investigating the use of metoprolol, a multicenter, randomized clinical trial was conducted to evaluate the effects of the medication in preventing vasovagal syncope in 208 patients with a mean age of 42 ± 18 years and a history of 9 syncopal events in 11 years (Sheldon et al., 2006). The results indicate that metoprolol did not provide sufficient efficacy in preventing vasovagal syncope in this population.

In another randomized clinical trial, 30 patients with recurrent vasovagal syncope and positive tilt test were evaluated (Flevari et al., 2002). Patients were randomized to receive propranolol, nadolol, or placebo in sequence, with each treatment lasting three months. The results showed that the central processes of propranolol did not significantly contribute to the therapeutic capacity of β-blockers in vasovagal syncope, suggesting that lipid-soluble and water-soluble drugs may have equivalent therapeutic efficacy. Interestingly, the study revealed that the peripheral processes of nadolol and propranolol are more clinically significant than the central mechanisms. The study findings indicate that lipophilicity and central nervous system action do not significantly improve the therapeutic efficacy of β-blockers.

3.2.3 Selective serotonin reuptake inhibitors (SSRIs)

The components of the Bezold-Jarisch reflex in the autonomic nervous system (ANS) are mainly serotoninergic (and also GABAergic) mediated. One hypothesis suggests the possibility of modifying the triggering responses of the reflex by directly or indirectly influencing the neurons involved to reduce the vasodepressor and/or cardioinhibitory action, decreasing the recurrence of syncope. Furthermore, as many of these drugs have anxiolytic qualities, it is possible to infer that they could also benefit the patient by decreasing the anxiety associated with the sudden episodes resulting in loss of consciousness.

Among the medications, a modest but significant impact was seen with fluoxetine and sertraline. Paroxetine, which appears to have the most significant therapeutic potential in its class, was evaluated in a randomized clinical trial that included 68 patients with recurrent syncope, positive tilt test results, and no neuropsychiatric comorbidities (Di Girolamo et al., 1999). The rate of syncope recurrence was 18% in the paroxetine-treated subjects, while in the placebo group, the rate was 53%. Although SSRIs present promising prospects for the treatment of syncope, it is still challenging to determine how much of the potential benefit stems exclusively from their effects on the vasovagal response and how much is due to their anxiolytic properties.

3.3 Cardioneuroablation

Cardioneuroablation is a medical procedure that eliminates or significantly reduces the vagal response, leading to symptom relief in 75% of patients (Carlos Pachon Mateos et al., 2020; Pachon M et al., 2011). No related complications were reported in follow-up studies lasting up to 14 years. Patients who underwent tilt testing within 4 months to one year after the procedure have also reported satisfactory reductions in syncope episodes. This procedure demonstrated promising results in managing symptoms related to autonomic dysfunction. Among the patient inclusion criteria for cardioneuroablation, the main one is the presence of reflex and/or bradyarrhythmia in symptomatic individuals free of existing heart conditions who have not responded to, or have some

contraindication to, non-invasive treatments. A pharmacological test is performed to confirm the reversibility of the condition through the patient's positive response to atropine.

3.4 Permanent Pacemaker (PPM)

The implementation of a definitive pacemaker, as studied in a randomized controlled trial with a population of 511 patients followed for an average of 12 months, demonstrated efficacy in reducing syncope episodes (Brignole et al., 2012). The study found that at least one-third of the population suffering from the syndrome achieved a reduction in their symptoms. However, the effectiveness of the intervention is more limited to mild and moderate cases, with less success in severe cases.

3.5 Closed-Loop Simulation (CLS)

A study published in the Journal of the American College of Cardiology found benefits of a technology provided by a German medical device company called closed-loop simulation (CLS), or closed-loop stimulation, which would be able to nullify the amount of syncope caused by vasovagal neurocardiogenic syndrome for approximately 19 months in a sample of 41 patients (Occhetta et al., 2004). The intervention monitors subtle changes in cellular electrical parameters and thus acts directly on the stimulation of the heart according to electrical stimuli, proving to be effective when indicated.

In summary, the proposed interventions' effectiveness can be found in the table below (Table 2).

Table 2. Assessment of improvement of syndromic neurocardiogenic vagal episodes

Methods	Efficacy	Targeted patients
Permanent pacemaker (PPM) (n = 1)	33% (absolute) and 57% (relative)	Non-severe syndromic adults
Cardioneuroablation (n = 2)	75%	Adults with reflex bradycardia
Aerobic physical training (APT) (n = 1)	72,7%	Adults with a recurring history of syncope
Pharmacological treatment (n = 6)	Reserved on a case-by-case basis	General population
Closed-loop stimulation (CLS) (n = 1)	100%	Severe and recurring syndromic adults
Tilt training (TTr) (n = 4)	19%	General population

4. Conclusion

Given the evaluation studies for the various forms of treatment for neurocardiogenic vasovagal syndrome, a wide variety of options can be identified, which, although heterogeneous, make it possible to visualize an evolution toward improving the prognosis of patients affected by VVS. The high rate of variability between efficacy and recurrence of cases among interventions is partly explained by the multifaceted aspect of the etiology and pathophysiology of this condition, the diversity in clinical manifestations, and the disparities in methodological approaches among the different studies. In conclusion, the management options for vasovagal neurocardiogenic syndrome (VVS) are evolving, and medical advances enable an analysis of the properties of each method to determine their best indications. It is essential to stress that the choice of treatment must be assessed by a specialist physician who has to approach each case individually to ensure the most appropriate and effective treatment for the particular clinical demands of each patient. As a result, the currently available interventions can significantly improve the quality of life of the population affected by this disorder. Further research is needed to understand the underlying mechanisms of vasovagal syncope better and develop more effective treatments for the condition. As a possible future direction for the study of the subject, further elaboration on early detection methods of vasovagal syncope is highly recommended for optimal management. In addition, further research could investigate the potential role of psychological interventions, such as cognitive behavioral therapy, in reducing symptom severity,

syncope recurrence, and improving the quality of life of individuals with VVS.

Regarding the limits of this study, it is essential to realize that some data cannot be directly compared due to the significant level of heterogeneity present among the patients who received therapy for VVS. Also, due to the limited number of studies that were picked for this analysis, there is a potential for bias in the selection process (however, efforts have been made to minimize this risk as much as feasible).

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Data Availability Statement

The data that support the findings of this study are available on request.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

References

Abuzainah, B., Gutlapalli, S. D., Chaudhuri, D., Khan, K. I., Al Shouli, R., Allakky, A., … & Hamid, P. (2022). Anxiety and Depression as Risk Factors for Vasovagal Syncope and Potential Treatment Targets: A Systematic Review. *Cureus, 14*(12), e32793. https://doi.org/10.7759/cureus.32793

Ali, M., Pachon Maetos, J. C., Kichloo, A., Masudi, S., Grubb, B. P., & Kanjwal, K. (2021). Management strategies for vasovagal syncope. *Pacing and Clinical Electrophysiology, 44*(12), 2100-2108. https://doi.org/10.1111/pace.14402

Brignole, M., Menozzi, C., Moya, A., Andresen, D., Blanc, J. J., Krahn, A. D., … & International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. (2012). Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation, 125*(21), 2566-2571. https://doi.org/10.1161/circulationaha.111.082313

Carlos Pachon Mateos, J., I Pachón Mateos, E., Higuti, C., Guilhermo Santillana Peña, T., Julio Lobo, T., Thiene Cunha Pachón, C., … & Amarante, R. (2020). Cardioneuroablation: Catheter Vagal Denervation as a New Therapy for Cardioinhibitory Syncope. *Journal of Cardiac Arrhythmias, 32*(3), 182-196. https://doi.org/10.24207/jca.v32n3.067_in

Di Girolamo, E., Di Iorio, C., Sabatini, P., Leonzio, L., Barbone, C., & Barsotti, A. (1999). Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *Journal of the American College of Cardiology, 33*(5), 1227-1230. https://doi.org/10.1016/s0735-1097(98)00694-9

Flevari, P., Livanis, E. G., Theodorakis, G. N., Zarvalis, E., Mesiskli, T., & Kremastinos, D. T. (2002). Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. *Journal of the American College of Cardiology, 40*(3), 499-504. https://doi.org/10.1016/s0735-1097(02)01974-5

Gajek, J., Zyśko, D., & Mazurek, W. (2006). Efficacy of tilt training in patients with vasovagal syncope. *Kardiologia Polska, 64*(6), 602-608; discussion 609-610. https://pubmed.ncbi.nlm.nih.gov/16810579/

Gampa, A., & Upadhyay, G. (2018). Treatment of Neurocardiogenic Syncope: From Conservative to Cutting-edge. *Journal of Innovations in Cardiac Rhythm Management, 9*(7), 3221-3231. https://doi.org/10.19102/icrm.2018.090702

Hussain, S., Raza, Z., Giacomini, G., & Goswami, N. (2021). Support Vector Machine-Based Classification of Vasovagal Syncope Using Head-Up Tilt Test. *Biology, 10*(10), 1029. https://doi.org/10.3390/biology10101029

Jang, W. J., Yim, H. R., Lee, S. H., Park, S.-J., Kim, J. S., & On, Y. K. (2013). Prognosis after tilt training in patients with recurrent vasovagal syncope. *International Journal of Cardiology, 168*(4), 4264-4265.

https://doi.org/10.1016/j.ijcard.2013.04.125

Kisanuki, M., Ikeda, S., Kondo, M., & Odashiro, K. (2022). A case of vasovagal syncope associated with carotid sinus hypersensitivity: Effectiveness of tilt training and subsequent squatting. *Journal of Cardiology Cases, 26*(6), 423-425. https://doi.org/10.1016/j.jccase.2022.09.003

Lakkireddy, D. (2019). Cardioneuroablation in the Management of Vasovagal Syncope, Sinus Node Dysfunction and Functional Atrioventricular Block: Patient Selection Based on Supporting Evidence. *Journal of Atrial Fibrillation, 13*(1). https://doi.org/10.4022/jafib.2396

Laranjo, S., Martins Oliveira, M., Tavares, C., Geraldes, V., Santos, S., Oliveira, E., Ferreira, R., & Rocha, I. (2012). O treino de ortostatismo (tilt training) aumenta a reserva vasoconstritora em doentes com síncope reflexa neurocardiogénica. *Revista Portuguesa de Cardiologia, 31*(7-8), 469-476. https://doi.org/10.1016/j.repc.2012.05.004

Occhetta, E., Bortnik, M., Audoglio, R., & Vassanelli, C. (2004). Closed loop stimulation in prevention of vasovagal syncope. Inotropy controlled pacing in vasovagal syncope (INVASY): a multicentre randomized, single blind, controlled study. *Europace, 6*(6), 538-547. https://doi.org/10.1016/j.eupc.2004.08.009

Pachon M, J. C., Pachon M, E. I., Cunha Pachon, M. Z., Lobo, T. J., Pachon M, J. C., & Santillana P, T. G. (2011). Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. *Europace, 13*(9), 1231-1242. https://doi.org/10.1093/europace/eur163

Romme, J. J., Reitsma, J. B., Black, C. N., Colman, N., Scholten, R. J., Wieling, W., & Van Dijk, N. (2011). Drugs and pacemakers for vasovagal, carotid sinus and situational syncope. *Cochrane Database of Systematic Reviews, CD004194*(10). https://doi.org/10.1002/14651858.CD004194.pub3

Schleifer, J. W., & Shen, W. (2015). Vasovagal syncope: an update on the latest pharmacological therapies. *Expert Opinion on Pharmacotherapy, 16*(4), 501-513. https://doi.org/10.1517/14656566.2015.996129

Sheldon, R., Connolly, S., Rose, S., Klingenheben, T., Krahn, A., Morillo, C., Talajic, M., Ku, T., Fouad-Tarazi, F., Ritchie, D., & Koshman, M.-L. (2006). Prevention of Syncope Trial (POST). *Circulation, 113*(9), 1164-1170. https://doi.org/10.1161/circulationaha.105.535161

Sheldon, R. S., Grubb, B. P., Olshansky, B., Shen, W.-K., Calkins, H., Brignole, M., … & Kanjwal, K. (2015). 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. *Heart Rhythm, 12*(6), e41-e63. https://doi.org/10.1016/j.hrthm.2015.03.029

Sheldon, R., Raj, S. R., Rose, M. S., Morillo, C. A., Krahn, A. D., Medina, E., … & Malcolm, V. M. (2016). Fludrocortisone for the Prevention of Vasovagal Syncope. *Journal of the American College of Cardiology, 68*(1), 1-9. https://doi.org/10.1016/j.jacc.2016.04.030

Takahagi, V. C. M., Costa, D. C., Crescêncio, J. C., & Gallo Junior, L. (2014). Physical Training as Non-Pharmacological Treatment of Neurocardiogenic Syncope. *Arquivos Brasileiros de Cardiologia, 102*(3). https://doi.org/10.5935/abc.20140021